II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 67 and 86-89 were pending prior to the Office Action dated September 9, 2003. Claims 67 and 86 have been amended. Support for the amendments may be found throughout the specification, for example, at page 17, lines 16-27, and in originally filed claim 25. No new matter has been added.

B. Claims Are Adequately Described

The Action rejects claims 67 and 86-89 as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Action argues that the claims contain "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Paper No. 19 at page 5. The Action also contends that the instant specification does not contemplate adenoviral vectors comprising a wild type p53 gene operably linked to a promoter or to a promoter that is a CMV, RSV, β-actin or SV40 promoter. Action at page 2. It concludes that the application is given a priority date of November 23, 1999—the date on which the instant application was filed. Applicant respectfully traverses this rejection.

As discussed in previous filings, the present specification adequately describes the invention to fulfill the written description requirement. The written description requirement is whether the "description clearly allows persons of ordinary skill in the art to recognize that he or she invented what is claimed." MPEP 2163.02 (citing *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989)). Applicant contends that it is clear that the specification describes what is claimed in rejected claims 67, 86-89. The claims are generally

directed to an "adenovirus vector comprising a wild type p53 gene under the control of a promoter." The written description of this application supports this claim and claims 67 and 87-89, which recite specific promoters. The specification makes clear that the inventor was in possession of the claimed invention:

- "In one specific embodiment, the invention concerns vector constructs for introducing wild type p53 genes (wt-*p53*) into affected target cells suspected of having mutant *p53* genes. These embodiments involve the preparation of a gene expression unit wherein the wt-*p53* gene is placed under the control of the β-actin promoter, and the unit is positioned in a reverse orientation into a retroviral vector." Specification at page 9, lines 6-12.

- In Example III, "The *p53* cDNA with its β-actin promoter was cloned into the LNSX retroviral vectors in ***both*** orientations." Specification at page 61, lines 29-30 (emphasis added).

- "While this affect [sic] was observed using the β-actin promoter and a retroviral expression vector, the inventors believe that this phenomenon ***will be applicable to other promoter/vector constructs for application in gene therapy***." Specification at page 8, line 25 to page 9, line 4 (emphasis added).

- "In addition to retroviruses, it is contemplated that ***other vectors can be employed, including adenovirus***...." Specification at page 14, lines 21-23 (emphasis added).

- "By way of illustration, but not limitation, one can mention the following bectors, including N2A, LN, LNSX, Adenovirus and Adeno-associated virus." Specification at page 33, lines 9-11.

- "While the **β-actin promoter** is preferred, the invention is by no means limited to this promoter and one may also mention by way of example promoters derived from **RSV**, N2A, LN, LNSX, LNSN, **SV40**, LNCX or **CMV**." Specification at page 15, lines 1-4 (citations omitted) (emphasis added).

- "***Generally speaking***, such a promoter might include either a human cellular or viral promoter. While the β-actin promoter is preferred the invention is by no means limited to this promoter...." Specification at page 14, line 35-page 15, lines 2 (emphasis added).

- "While the retroviral construct aspect of the invention concerns the use of a β-actin promoter in reverse orientation, there is no limitation on the nature of the selected gene which one desires to have expressed. Thus, the invention concerns

the use of antisense-encoding constructs ***as well as 'sense' constructs that encode a desired protein.***" Specification at page 16, lines 5-10.

Therefore, the specification *as a whole* makes clear that 1) p53 sense constructs are contemplated in both orientations; 2) any discussion about antisense constructs applies to "sense" constructs such as p53; 3) constructs can be retroviral, but they may also be adenovirus constructs, and thus, are not limited to retroviruses; 4) promoters are discussed both generally and in the context of antisense constructs, in addition to CMV, RSV, and SV40 being specifically mentioned; and finally, 5) because an adenovirus can be used instead of retrovirus and since constructs are not limited to antisense constructs, applying equally to sense constructs, there is adequate written description for an "adenovirus vector comprising a wild type p53 gene under the control of a promoter," as well as for vectors with a CMV promoter.

The Action goes through each citation individually to argue that there is no written description for the claimed invention. However, the issue is whether the disclosure as a whole indicates that Applicant was in possession of the invention. As shown above, the skilled artisan would recognize that embodiments discussed in the application could be practiced in the context of a pharmaceutical composition of adenovirus and with the recited promoters to express a wild type p53 gene. Therefore, as a whole, the application supports the claimed invention.

In addition to the Declaration of Dr. Lou Zumstein, submitted with the Response filed on October 18, 2001, Applicant submitted the Declaration of Dr. Philip Hinds with the CPA filed on May 13, 2002. Both of these constitute evidence from a person of ordinary skill in the art to support the contention that the Applicant was in possession of the claimed invention at the time the priority application was filed. Applicant contends that the Action has not rebutted the evidence submitted by persons of ordinary skill in the art to maintain the rejection of these claims. Such evidence meets the "preponderance of the evidence" standard set forth in MPEP §

2163.04. The declarations and the identified portions of the specification show the written description requirement has been met. Accordingly, Applicant respectfully requests this rejection be withdrawn.

The Action contends that in the places where adenovirus or promoters claimed are disclosed, "each such disclosure is within the context of antisense RNA production." Office Action page 6. Applicant denies that adenoviruses are discussed in the application only in the context of antisense embodiments. The paragraph in which the Specification discloses that other vectors such as adenovirus can be used instead of a retrovirus begins, "In broader aspects of the invention, a preferred approach will involve the preparation of retroviral vectors which incorporate nucleic acid sequences encoding the desired construct, once introduced into the cell to be treated...." Specification at page 14, lines 9-12. The use of adenovirus is discusses in the context of "broader aspects of the invention," and retroviruses and antisense constructs are but examples of aspects of the invention. Similarly, as quoted above, the following paragraph discussing promoters indeed recites particular embodiments of the invention, such as antisense; however, it says, "***Generally speaking***, such a promoter might include either a human cellular or viral promoter. While the β-actin promoter is preferred the invention is by no means limited to this promoter...." Specification at page 14, line 35-page 15, lines 2 (emphasis added).

Because the Specification indicates to a skilled artisan that the inventor was in possession of the claimed invention at the time the application was filed, Applicant respectfully requests this rejection be withdrawn. Furthermore, because the application complies with 35 U.S.C. §112, the claims are entitled to the benefit of their priority date of October 13, 1992. 35 U.S.C. 120.

C. Claims 67 and 86 Are Not Anticipated under § 102 (b)

The Action rejects claims 67 and 86 as unpatentable over Liu *et al.* (1994) ("Liu") based on 35 U.S.C. § 102(b). It contends that Liu anticipates the claimed invention. Applicant respectfully traverse this rejection.

As discussed above, the present application is entitled to claim priority to U.S. Application ('513 application), filed October 13, 1992. Accordingly, claims 67 and 86 are not anticipated by Liu because it is not prior art against the claimed invention. Liu was published in 1994, while the present application is entitled to a priority date that precedes the Liu publication date. Because Liu is not prior art against the application, it cannot anticipate the claimed invention. Consequently, Applicant respectfully requests this rejection be withdrawn.

D. Claims 86-89 Are Not Obvious

The Action rejected claims 86-89 as obvious over the references of Chen *et al.* (1990) ("Chen reference") and Stratford-Perricaudet *et al.*. *Human Gene Therapy* 1, 241-256 (1990) ("Stratford-Perricaudet reference") in view of Wilkinson *et al.* (Wilkinson), Colicos *et al.* (Colicos), Rajan *et al.* (Rajan), and Hitt *et al.* (Hitt).

The claims are directed generally to an "adenovirus vector comprising a wild type p53 gene under the control of a promoter [CMV, RSV, β-actin, and SV40], wherein the vector is comprised in a pharmaceutical composition."

1. No reasonable expectation of success

To render claims obvious, the relied upon references must also "reveal that in so making or carrying out, those of reasonable skill would have a reasonable expectation of success." *In re Vaeck*, 20 U.S.P.Q. 2d 1438, 1443 (Fed. Cir. 1991) *citing In re Dow Chemical Co.*, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988).

In this case, the "expectation" issue here concerns what those of skill in the art would have predicted, *a priori*, regarding the ability of adenovirus to express p53, particularly in a therapeutic context as the claims recite a "pharmaceutical composition" and that is what the Examiner has relied upon as the basis for the motivation or suggestion to combine references. As discussed in previous responses, the cited references do not teach that the claimed invention can be made **and used**. Moreover, the Action concedes that "[w]hat Jaffee, and Rosenfeld, teaches is that for methods of therapy, the administration of Ad-p53 would be unpredictable...." Action at page 17. Equally true is that those references indicate that pharmaceutical compositions comprising Ad-p53 are similarly unpredictable. Applicant notes that it has been the Patent Office's practice not to restrict pharmaceutical compositions from methods of treating using those pharmaceutical compositions. In an application related to the present case by priority, the U.S.P.T.O. took the position that gene therapy was "extremely poorly developed," noting that "adenoviral vectors are potentially dangerous for use in humans because several adenoviral genes have been shown to influence tumor formation in experimental animals and are associated with malignant transformation of cells in culture. . . ." Office Action in USN 08/459,713 (see Appendix F submitted with Response filed on July 28, 2003 with RCE) relying on Orkin *et al.* (Exhibit A). This is further evidence for the lack of expectation of success at achieving the claimed invention.

Furthermore, there was a lack of expectation of success in producing the claimed vector because, as argued previously, in the early 1990s it was unknown whether an adenovirus vector encoding p53 could be made because p53 was known to bind E1B (see, for example, Fields) (Exhibit B). To produce the virus requires a host cell, which would express both proteins. Therefore, there was no reasonable expectation of even *producing* the vector.

The Action contends that "if the presence of E1B is so deleterious that vector production is inhibited, applicant should limit their claim to an E1B-adenovirus." However, the issue is not whether only an E1B- adenovirus would work, but whether there was a reasonable expectation of success in producing a p53-encoding adenoviral vector, given that this situation requires expression of E1B and p53—two proteins that associate with each other—in a cell together.

2. Obvious to try is an improper basis for a rejection

The Action contends that it would have been obvious to the ordinary artisan at the time of the present invention "to produce the claimed vectors for assessment of their *in vivo* expression potential." Action at page 14. However, this sounds like an "obvious to try" argument, which is improper. *See Jones v. Hardy,* 220 USPQ 1021, 1026 (Fed. Cir. 1984). According to *In re Eli Lilly & Co.,* 14 USPQ2d 1741, 1743 (Fed. Cir. 1990), "[a]n 'obvious to try' situation exists when . . . further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result or indicate that the claimed result would be obtained if certain directions were pursued." The cited references fail to indicate that sufficient expression of p53 could be achieved in the context of an adenovirus vector and thus, qualify as promoting the attempt toward attaining the claimed invention, but nothing more.

Accordingly, Applicant contends that the vector claims are patentable over the cited references, and respectfully requests the withdrawal of this rejection for claims 86-89.

3. The claimed invention produced surprising and unexpected results

The claimed invention is directed to pharmaceutical compositions of adenoviral vector compositions comprising p53 in the context of gene therapy. As argued previously, the PTO has widely espoused the view that gene therapy is an unpredictable area. Applicant provided a statement from Examiner Guzo in a case related by priority to the present application (USN 08/459,713) and they provided a declaration from Deborah R. Wilson to show that the claimed

invention achieves the surprising and unexpected result of clinical efficacy.[1] That any gene therapy is successful constitutes a surprising and unexpected result that could not have been predicted based on the prior art cited in this case. The prior art does not provide evidence of clinical efficacy and instead merely provides basic tools that the skilled artisan is expected to combine to create the claimed invention.

The clinical evidence previously filed demonstrates the therapeutic value of adenovirus p53 compositions, which could not have been predicted based on the cited prior art. As such, this is additional evidence to rebut the contention that the claimed invention is obvious.

4. Issued and Allowed Claims Concerning Ad-p53

Applicant also notes that several patents have issued and an additional number of claims in pending patent applications have been allowed that involve adenovirus vectors expressing p53. These patents and patent applications claim priority to the same application for which priority is claimed in the present application.

A list of these patents and patent applications are included herewith, along with copies of what Applicant's representative believes are the allowed or issued claims (Exhibit C).

1) U.S. Pat. No. 6,410,010
2) U.S. Pat. No. 6,511,847
3) U.S. Pat. No. 6,143,290 (same Examiner as present case)
4) U.S. Serial No. 08/626,678
5) U.S. Serial No. 08/459,713
6) U.S. Serial No. 09/413,109

This list is further evidence that the claimed invention is novel and nonobvious over the cited prior art. Accordingly, Applicant respectfully urges that this rejection be withdrawn.

---

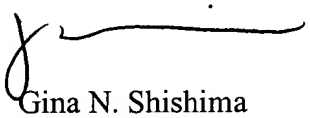
[1] The Action contends that the declaration is deficient because it does not disclose what adenoviral construct "INGN 201" is. Applicant has included documentation that indicates INGN 201 is now being marketed by the licensee, Introgen Therapeutics, as Advexin®, and that the vector is described in a number of issued patents, for example, U.S. Patent 6,410,010, which

CONCLUSION

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejections of all claims be withdrawn so they may pass to issuance.

Should the Examiner desire to sustain any of the rejections discussed in relation to this Response, the courtesy of a telephonic conference between the Examiner, the Examiner's supervisor, and the undersigned attorney at 512-536-3081 is respectfully requested.

Respectfully submitted,



Gina N. Shishima
Reg. No. 45,104
Attorney for Applicant

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 474-5201
(512) 536-4598 (facsimile)

Date: February 9, 2004

---

claims priority to the same application as the current application (USN 07/960,513). *See* Exhibit D.